Thermal Racemization of (+)-Bicyclo[2.2.1]hept-5-ene-*trans*-2,3-dicarboxylic Acid in the Melted and Solid States[1]

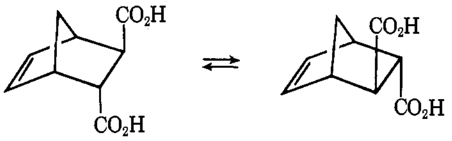
Richard E. Pincock,* Min-Min Tong, and Keith R. Wilson

Contribution from the Department of Chemistry, University of British Columbia, Vancouver 8, British Columbia, Canada. *Received July 20, 1970*

Abstract: The thermal racemization of polycrystalline samples of neat (+)-bicyclo[2.2.1]hept-5-ene-*trans*-2,3-dicarboxylic acid (mp 176°) has been studied from 130 to 194°. Up to 165° the reaction occurs in the solid state ($\Delta H^{\ddagger} = 40.0$ kcal/mol, $\Delta S^{\ddagger} = 14$ eu) at a rate only *ca.* one-tenth of the melt rate extrapolated to these temperatures (for the melt at 176–194°, $\Delta H^{\ddagger} = 29.7$ kcal/mol, $\Delta S^{\ddagger} = -6.9$ eu). The strictly first-order solid-state reaction has no inhibition period and is unaffected by crystal size or optical purity of samples. This reverse Diels–Alder reaction and recombination occur throughout the bulk of polycrystalline sample rather than at crystal defects or impurity sites. X-Ray diffraction patterns of partially racemized samples taken from runs below the eutectic temperature of 165° show growth of (±)-racemic compound (mp 186°). From 165 to 176° (*i.e.*, in the region where melt $\rightleftarrows$ solid equilibrium is attained) the racemization shows autoacceleration and sigmoid shaped kinetic curves characteristic of concurrent two-phase reactions.

It has commonly been remarked that there are a few studies of thermal isomerization reactions of organic solids.[2] Qualitative observations that decompositions or isomerizations of some organic compounds occur only "on melting" enforce the feeling that the corresponding solid state reactions are usually negligibly slow. Some experimental evidence for this has been reviewed by Morawetz.[2b] He presented the few examples which indicate that rates in solids are usually much slower (by 10^3–10^4) than the same reaction in a solution phase.

On the other hand, endo to exo isomerization of the maleic anhydride–cyclopentadiene adduct occurs with equal facility in either its solid state or in a melted phase.[3] This unusual result prompted a study of a related possibility—the racemization of the optically active compound **1** in the solid state.



1, (+) enantiomer (mp 176°), (±) racemate (mp 186°)

It was of interest to see if thermal racemization could occur below the melting points of enantiomer or of the racemate and, if so, whether it occurs throughout the sample, in crystal defects, or only in liquid regions developing in a polycrystalline sample. The rate in a neat, melted phase could hopefully be obtained for comparison with any solid-state reaction.

Even the kinetic forms of such solid-state isomerizations are unpredictable; for example, they could be subject to some of the complexities of most solid-state inorganic reactions[4] (often multistep processes very dependent on crystal size or surface, on impurities, and on previous treatment of samples). There are suggestions[5] and some recent illustrations[6,7] that solid-state reactions may be used to exercise control on product distribution and stereochemistry of organic reactions. Kinetic studies, such as on the simple isomerization of compound **1**, may further expand potential applications of the organic solid state.

Results and Discussion

Racemic *trans*-diacid (**1**) was resolved by multiple recrystallizations of its brucine salt.[8] The constant rotation finally obtained was much greater than previously reported and the melting point of regenerated acid was also 10° higher than that of previously resolved samples.[8] Although it is of course possible that the resolution is still incomplete, it turned out that even the solid-state kinetic results (below) do not depend on the optical purity of samples.

Racemization in the Melt and in Solution. For comparison with the rate of racemization in the solid, the rate in neat, melted samples of (+)-**1** (mp 176°) was obtained from 176 to 194° (see Table I). As expected, first-order plots of log α/α_0 against time were straight lines. The first-order rate constants obtained are of the order expected from similar reverse Diels–

---

[1] Research sponsored by the Canadian National Research Council and by the U. S. Air Force Office of Scientific Research, Grant No. AFOSR 1102-66.

[2] (a) C. E. H. Bawn, "Chemistry of the Solid State," W. E. Garner, Ed., Butterworths, London, 1955, p 254; (b) H. Morawetz, "Physics and Chemistry of the Organic Solid State," Vol. I, D. Fox, M. M. Labes, and A. Weissberger, Ed., Interscience, New York, N. Y., 1963, Chapter 4 (and Addendum, Vol. II, p 853); (c) R. T. Puckett, C. E. Pfluger, and D. Y. Curtin, *J. Amer. Chem. Soc.*, **88**, 4637 (1966).

[3] R. E. Pincock, K. R. Wilson, and T. E. Kiovsky, *ibid.*, **89**, 6890 (1967).

[4] *Cf.* (a) D. A. Young, "Decomposition of Solids," Pergamon Press, Oxford, 1966, Chapter 1; (b) "Reactivity of Solids," J. H. deBoer, *et al.*, Ed., Elsevier, Amsterdam, 1961; (c) see also, for example, T. A. Clarke, E. L. Evans, K. G. Robbins, and J. M. Thomas, *Chem. Commun.*, 266 (1969); Y. Halpern, M. Michman, and S. Patai, *J. Chem. Soc. B*, 149 (1966).

[5] (a) M. M. Labes, H. W. Blakeslee, and J. E. Bloor, *J. Amer. Chem. Soc.*, **87**, 4251 (1965); (b) H. Morawetz, S. Z. Jakabhazy, J. B. Lando, and J. Shafer, *Proc. Nat. Acad. Sci. U.S.*, **49**, 789 (1963).

[6] K. Penzien and G. M. J. Schmidt, *Angew. Chem.*, **81**, 628 (1969); G. Brenner, F. E. Roberts, A. Hoinowski, J. Budavari, B. Powell, D. Hinkley, and E. Schoenewaldt, *ibid.*, **81**, 1046 (1969); E. L. Allred and R. L. Smith, *J. Amer. Chem. Soc.*, **91**, 6766 (1969); P. D. Bartlett, G. N. Fickes, F. C. Haupt, and R. Helgeson, *Accounts Chem. Res.*, **3**, 177 (1970).

[7] For reviews of stereoselective solid-state polymerizations, see H. Morawetz, *Science*, **152**, 705 (1966), and ref 2b; see also "Organic Solid State Chemistry," G. Adler, Ed., Gordon and Breach, New York, N. Y., 1969, Chapter 6. Stereospecific solid-state photochemical reactions are well established; see G. M. J. Schmidt in "Reactivity of the Photoexcited Organic Molecule," Interscience, New York, N. Y., 1967, p 227.

[8] A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).

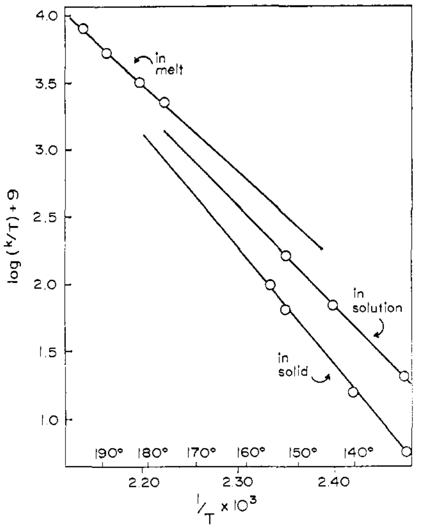


Figure 1. Relation of log (k/T) to reciprocal temperatures for racemization of (+)-enantiomer **1** in melted, solid, and solution (in tetralin) phases.

Alder reactions.[9] Although heating of neat diacid above its melting point results in some polymerization, racemization is the initial reaction. Just above the melting point the racemization is rapid (half-life *ca.* 10 min) suggesting that even if the lower temperature solid-state reaction is greatly slower, it might still be quantitatively measured and compared.

Table I. First-Order Rate Constants for Racemization of (+)-**1** in Solid, Melt, and Solution

Temp, °C	$k \times 10^5$, sec^{-1}	Temp, °C	$k \times 10^5$, sec^{-1}
194.3	380[a]	166.2	8.3[b,c]
189.1	248[a]	161.2	7.09[b,c]
181.8	147[a]	155.4	4.23[c]
176.6	103[a]	152.4	2.76[c]
152.4	6.98[d]	140.2	0.654[c]
143.7	2.93[d]	130.9	0.227[c]
131.3	0.834[d]		

[a] Neat, completely melted samples. [b] Initial rate constant (see text and Figure 4). [c] Neat, polycrystalline samples. [d] *Ca.* 0.27 M in tetralin.

For comparison at temperatures where pure **1** would be solid, the rate of racemization of (+)-**1** was also obtained in solution. In tetralin (0.27 M **1**) at 131–152° the rate of racemization is 2.5–2.0 times slower than the melt rate extrapolated down to these temperatures (see Figure 1). Consistent with the racemization as a reverse Diels–Alder reaction and recombination, the rate of loss of optical activity is subject to only a small solvent effect on changing from melt to nonpolar tetralin.[10] Like the reaction in the melt, the thermal racemization in tetralin solution is much more rapid than any side reactions leading to polymeric material.

Racemization in the Solid State. To establish the existence of a true solid-state reaction it was necessary to determine the range of temperatures for existence of solid states at all compositions of pure (+)-**1** to pure racemic (±)-**1**. The phase diagram of the two component system was investigated by means of differential scanning calorimetry on samples with various compositions of (+) and (±) acid. Endotherms at 165° for a wide range of compositions showed this as the eutectic temperature with a eutectic composition of about 25% (+), or, in other words 50% racemized. The phase relationship is as in Figure 2, which is similar to the well-known example of (+)- and (−)-tartaric acids; the racemate melts higher than the resolved acid and a "simple" eutectic[11] is formed between resolved and racemic compounds. Below 165° all mixtures of (+) and (−) acid are solid, while above 165° to the melting points of pure (+) (at 176°) and pure racemate (at 186°) a solid compound is in phase equilibrium with a liquid mixture of (+) and (−) acids.

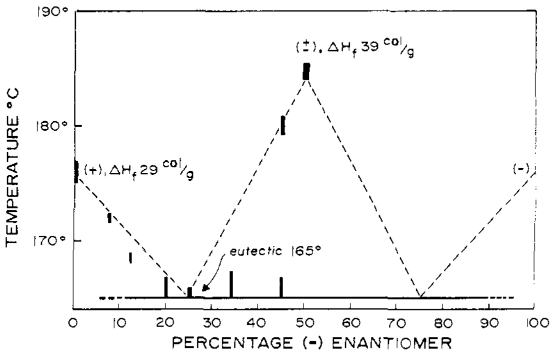


Figure 2. Phase relationship of mixtures of (+)- and (−)-enantiomers of compound **1**. Vertical lines indicate temperature ranges of endotherms determined by differential scanning calorimetry.

The rate of racemization in neat, polycrystalline (+)-**1** was followed in the temperature range from 130 to 176°. Individual sealed samples (*ca.* 30 mg each) were withdrawn at various times, cooled, and dissolved in acetone for polarimetric analysis. Below 155° the racemization proceeded without kinetic complications of any sort, *e.g.*, the inhibition times which are often characteristic of solid-state reactions were absent. Also any dependency on past history of the sample, which is a common feature of many inorganic solid-state reactions,[4] was also absent. The rate was unaffected by grinding samples, unchanged by use of different batch preparations, and independent of the extent of resolution of samples.

The simplicity of the kinetics for this solid-state reaction is shown in Figures 3 and 4. First-order plots of log (specific rotation) against time were straight to over 90% racemization. Aside from a slight yellowing (*e.g.*, after 8 half-lives for racemization at 152°) the (+)-**1** acid, mp 176°, transformed smoothly in the solid state to pure (±)-**1** of mp 185°. The transformation was also qualitatively monitored by X-ray powder photographs of partially racemized material. At *ca.* 50% racemization, diffraction rings characteristic of both resolved (+)-**1** and racemic (±)-**1** could be observed. The complete solid-state reaction proceeds,

---

[9] J. A. Berson and A. Remanick, *J. Amer. Chem. Soc.*, **83**, 4947 (1961); J. E. Baldwin and J. D. Roberts, *ibid.*, **85**, 115 (1963).

[10] Diels–Alder reactions and retrogressions show only small solvent effects; *cf.* A. Wassermann, "Diels–Alder Reactions," Elsevier, Amsterdam, 1965, Chapter 4.

[11] The labeling of this pseudobinary system as a simple eutectic with compound formation (the racemate) is perhaps an oversimplification. One should recognize that narrow single-phase regions of solid solution will exist toward the edges of the diagram. When very small these regions will be difficult to detect by calorimetry, as is the case here.

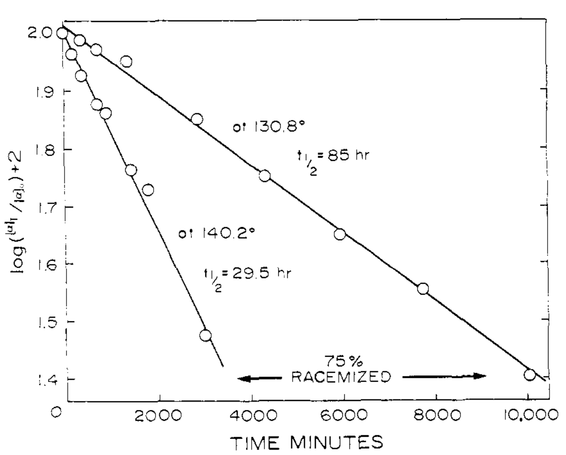


Figure 3. First-order kinetic plots for racemization of neat, polycrystalline (+)-**1** in the solid phase.

not through a single phase solid solution as is the case with endo–exo isomerization noted previously,[3,12] but by growth of a separate phase of solid (±)-racemate from solid (+)-enantiomer.

Mechanism in the Solid State. The contrasts between the kinetic simplicity of this reaction from 130 to 155° and the complexities of some other organic solid-state reactions are worth pointing out. Induction periods[13] and autocatalytic effects,[14] sigmoid-shaped kinetic curves,[15] and dependency on aging and on particle size[16] have all been common observations for various solid-state reactions. Some features such as sigmoid curves and autocatalysis may often be caused by growth of a liquid phase[14,17] (see below). However, the part of reaction which is a true solid-state reaction has not been reported to be as kinetically simple as the first-order racemization of (+)-**1**. Apparently this racemization occurs throughout the bulk of solid sample and, unlike most solid-state reactions, is not dependent on the presence nor growth of crystal defects. The first-order kinetics show that each molecule of the solid has equal probability of thermal reaction, just as in a melted state.

However, the first-order rate of reaction in the solid phase at 130–155° is *ca.* ten times slower than the extrapolated rate in the melted phase (see Figure 1). The activation parameters also differ widely ($\Delta H^{\ddagger}$ = 40.0 kcal/mol, $\Delta S^{\ddagger}$ = 14 eu for the solid; $\Delta H^{\ddagger}$ = 29.7 kcal/mol, $\Delta S^{\ddagger}$ = −6.9 eu for the melt). This rate factor of ten is considerably less than those observed for previous comparisons of solid and melt (or solution) reactions.[2] As mentioned above, reverse Diels–Alder reactions and recombinations are relatively insensitive to solvents or catalysts; the small rate difference between solid and melt may be likened to a small solvent effect. There is, however, a distinct energy difference between (+)-**1** in the solid and in the melt and this must be considered.

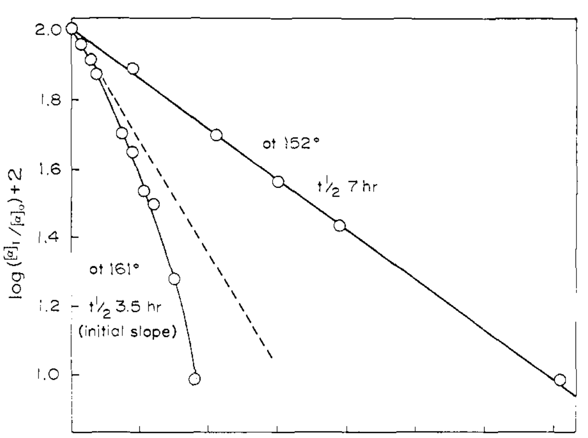


Figure 4. First-order kinetic plots for racemization of neat polycrystalline (+)-**1** at 152° in the solid phase and at 161° nearer the melting point.

A quantitative relationship between melt and solid-state rate constants suggested at an early date by Hinshelwood[18] is $\ln(k_l/k_s) = \Delta H_{\text{fusion}}/RT$. This equation neglects entropy factors and assumes that the transition state is the same in both solid- and liquid-state reactions. From the heat of fusion of (+)-**1** of 29.5 cal/g the rate difference is predicted to be $k_l/k_s = 6 \times 10^2$ at 150°. This is considerably greater than the observed factor of 10, but in any case a general kinetic relationship of solid reaction to liquid reaction cannot be this simple. An equation based on the free-energy difference of solid and liquid states, which also assumes the same transition state for solid and liquid reactions, is $\ln(k_l/k_s) = (G_l - G_s)/RT$.[3] By using the measured heat of fusion of (+)-**1** to approximate the enthalpy and entropy changes near the melting point of **1**, the equation gives a rate ratio of k_l/k_s = 1.5 at 150°. This is at least closer to the observed value.

However, in general, the transition state (as well as initial state) in the solid reaction may be different from that in the liquid state. For example, unique solid-state stereochemistry might show up as large and stereospecific (with retention) cage effects. In the racemization of compound (+)-**1** this would result in a decreased relative rate of racemization in the solid. Since the observed rate difference is only a factor of 10, such a stereospecific cage effect is probably absent. The (+)-diacid **1** dissociates without appreciable kinetic hindrance in the solid to cyclopentadiene and fumaric acid. These rotate, recombine, and then interact with enantiomer to form the racemic (+) compound. At low conversions the racemic compound produced by this reaction will very likely exist in solid solution with the (+)-enantiomer. Further production of racemic compound will eventually render the dilute solid solution unstable (*i.e.*, supersaturated). This supersaturation is the driving force for the nucleation and production of a separate phase of racemic compound. The kinetic simplicity of the reaction indicates that this phase change is fast compared to enantiomer conversion in the solid (+)-acid phase. From the relative changes in activation parameters for solid ($\Delta H^{\ddagger}$ = 40.0 kcal/mol, $\Delta S^{\ddagger}$ = 14 eu) and melt ($\Delta H^{\ddagger}$ = 29.7 kcal/mol, $\Delta S^{\ddagger}$ = −6.9 eu) reaction, it seems that racemization in the solid involves energeti-

---

(12) R. E. Pincock, *Accounts Chem. Res.*, **2**, 97 (1969).

(13) S. Patai and Y. Gotshal, *J. Chem. Soc. B*, 489 (1966).

(14) D. F. Debenhan, A. J. Owen, and E. F. Pembridge, *ibid.*, *B*, 213, 675 (1966).

(15) A. D. Yoffe, *Proc. Roy. Soc., Ser. A*, **208**, 188 (1951).

(16) W. D. Burrows, *J. Org. Chem.*, **33**, 3507 (1968).

(17) R. E. Pincock and T. E. Kiovsky, *Chem. Commun.*, 864 (1966).

(18) C. N. Hinshelwood, *J. Chem. Soc.*, **119**, 721 (1921).

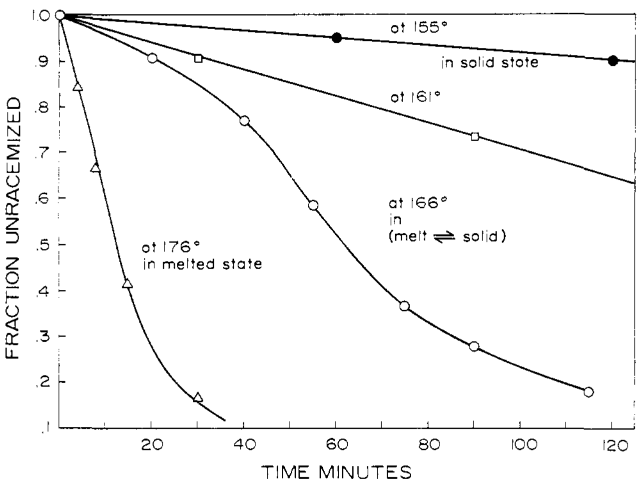


Figure 5. Kinetic data for racemization of neat samples of (+)-**1** in the solid (155°), in the biphase system at 166° (where melt ⇌ solid), and in a completely melted system (at 176°).

cally unfavorable but entropically favorable disruption of the crystal around the transition state.

This solid-state reaction indicates that certain thermal reorganization reactions may not be appreciably kinetically hindered in the solid state. It may be that such facile solid reactions, together with possible stereospecific features,[19] may lend special interest to further examples of thermal solid-state isomerizations.

Concurrent Reactions in Melt and Solid. Above the eutectic temperature of 165° where solid (+) is in equilibrium with melt, simultaneous reactions must occur in both liquid and solid states. This leads to the sigmoid-shaped curves (see Figure 5 at 166°) observed for biphase, "frozen state" reactions of solids.[12,17] The greater rate of reaction in the melt and the autocatalytic growth in volume of this phase results in departure from the first-order kinetics of the pure solid reaction. The onset of this is shown at 161° in Figure 4 by the downward curvature from the first-order line. This may reflect a softening of the crystal just below the melting point of eutectic. More likely, impurities are developed which partially melt the solid (some sintering of the samples was observed at this temperature); indeed, at 161° the samples darken much more rapidly than at higher temperatures in totally melted runs. The individual contributions of solid and melted phase reactions to the overall observed racemization can, in principle, be separated.[3,12] However, in this case the availability of data on both pure solid and pure melt runs makes this unnecessary.

Experimental Section

(±)-Bicyclo[2.2.1]hept-5-ene-*trans*-2,3-dicarboxylic Acid. Compound **1** was prepared from fumaric acid and cyclopentadiene in refluxing 0.1 *M* sulfuric acid.[20] Recrystallization from water (with charcoal decolorization) gave colorless solid, mp 186–187° (lit. mp 187–188°,[20] 186–187°[8]). No water of hydration is present.

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.35; H, 5.60.

Resolution of 1. The (+)-enantiomer of **1** was obtained by crystallization of its brucine salt.[8] Rather than recrystallizations from water, multiplet recrystallizations from 80% acetone–20% water by volume seemed more efficient and ultimately (after *ca.* 20 cycles) gave more highly resolved product. The acid was regenerated by treatment of the salt with 5 *M* NaOH, filtering off the brucine, and acidifying the filtrate. Recrystallization from water gave (in different preps) material of rotations $[\alpha]^{26}\text{D}$ +147 and +137° (in acetone), with mp 177–179 and 176–178° (lit.[8] $[\alpha]^{20}\text{D}$ +89°, mp 166–168°).

Kinetic Methods. A. Solid Phase. For the kinetics of racemization of neat, crystalline material, a set of weighed samples of resolved (+)-**1**, *ca.* 30 mg each, in 2-ml sealed vials was completely immersed in a constant-temperature silicone oil bath. At an appropriate time an individual sample was withdrawn and cooled to room temperature. Each sample was completely dissolved in acetone and transferred to a 2-ml volumetric flask which was then diluted up to the mark. Optical rotations were obtained at the sodium line using a 1-cm length cell and a Bendix Type 143A automatic polarimeter calibrated with known standard sucrose solutions. A specific rotation $[\alpha]_{t=\text{time}}$ was then calculated for each sample of the set. First-order rate constants (*k*) were obtained by plotting $\log([\alpha]_t/[\alpha]_{t=0}) + 2$ against time; $k = 2.303(\text{slope of line})$. Runs at 131 to 155° gave straight first-order plots as far as followed (up to 90% racemization); kinetic plots for runs at 161 and 166° were curved within 30% reaction indicating an accelerative effect. Samples remained colorless and crystalline except at higher temperatures (160°) where some yellowing near the end of the run occurred.

B. Melted Phase. The rate of reaction in the melted phase was obtained with samples prepared and analyzed in the same manner as with runs below the melting point. In the melt, racemization was complete before any significant yellowing of samples occurred.

C. Solution Phase. The rate of racemization in tetralin solution was obtained using a set of sealed vials for each run. Each contained a weighed amount (*ca.* 10 mg) of (+)-**1** and 0.2 ml of purified tetralin. The acid dissolved only when the samples were heated for the run; concentrated solutions (*ca.* 0.27 *M*) were thereby possible. After removal from the constant-temperature bath at various times, the samples were diluted to 2 ml with acetone and the optical rotations were measured.

Product Studies. (+)-Racemic acid was heated in tetralin at 140° for 96 hr (which is greater than 15 half-lives for racemization of (+)-acid). Extraction of the acid into 10% NaOH and acidification gave (±)-acid whose nmr spectrum was identical with that of original acid. No fumaric acid signal was present in the spectrum. In another run 0.45 g of (±)-acid was heated with 10 ml of tetralin at 140° for 52 hr (*ca.* 9 half-lives). On cooling 0.32 g (71%) of (±)-acid was recovered, mp 180–184°. Extraction of mother liquors with dilute base gave 0.094 g (21%) of sticky, probably polymeric, solid. Essentially complete interconversion of enantiomers occurs before side reactions become important at long reaction times.

Phase Diagram. Calorimetric data were obtained using a Perkin-Elmer differential scanning calorimeter DSC-1B with heats of fusion calibrated with a standard indium sample. To determine the eutectic point of the (+) and (−) system, samples of (+)-acid were racemized to various known extents by heating various times at 151°. When analyzed by dsc, the samples containing 13, 19, 25 34, and 45% total (+) isomer all showed endotherms corresponding to a eutectic point at 165–167°. The 25% sample showed only a single symmetrical endotherm with a maximum heat change at 165°; thus the eutectic composition of roughly 25% (+) (*i.e.*, 50% racemized) was indicated. Pure racemate (50% (+) isomer) showed only a fusion endotherm at 184–186° with ΔH_{fusion} of 39.1 ± 1.3 cal/g; the (+) enantiomer showed fusion at 175–177° with $\Delta H_{\text{fusion}} = 29.5 \pm 0.9$ cal/g.

Acknowledgment. We thank the Alfred P. Sloan Foundation for a Fellowship to R. E. P. and the National Research Council, and the H. R. MacMillan Family Fund (University of British Columbia) for Fellowships to K. R. W.

---

[19] R. E. Pincock and K. R. Wilson, *J. Amer. Chem. Soc.*, **93**, 1291 (1971).

[20] H. Koch, J. Kotlan, and H. Markut, *Monatsh. Chem.*, **96**, 1649 (1965).